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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,731	04/26/2005	Serge Auvin	427.095	6471

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EXAMINER	
HABTE, KAHSAY	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,731	AUVIN ET AL.	
	Examiner	Art Unit	
	Kahsay Habte	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4 and 11-14 are pending in this application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising a compound of formula (I) or a method of treating cataract, muscular dystrophy and osteoporosis, does not reasonably provide enablement for a pharmaceutical composition and method of inhibition of calpains and lipid peroxidation; or the rest of the diseases recited in claim 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual

determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant composition claim 11 recites a particular intended use for the composition, i.e., 'for inhibition of calpains and lipid peroxidation', which according to the specification is directed to a wide list of therapeutic methods and the specification, does not provide enablement for all the listed disorders. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

The instant claims 12-13 are drawn to 'a method of inhibiting calpain' and 'a method of inhibiting lipid peroxidation' respectively. The specification at pages 42-44 provides pharmacological procedures to study the effects of the compounds, however, there is no test data or inhibition results provided for any the compounds of the instant claims. As the instant claim recites 'a method of inhibiting calpains' and 'a method of inhibiting lipid peroxidation' in warm-blooded animals', the claim is directed to 'a method of treating a disease mediated by the enzymes' and the specification provides an exhaustive list of diseases that are associated with the potential role of calpains and ROS's, see pages 1-2. The instant claims appear to be a 'reach through' format. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or

conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The testing assays provided in the specification on pages 38-40 are related to inhibition of calpains and the inhibition of lipid peroxidation and the instant claims are drawn to 'a method of treating a disorder slected from the groups consisting of inflammatory and immunological diseases, cardio-vascular diseases and cerbero-vascular disease, disorders of the central or peripheral nervous system..., proliferative disease, ... and viral diseases' in warm-blooded animals', however, there is neither data on how many compounds were tested nor data on which enzymes were inhibited and which ones were not. Applicant did not state on record or provide any guidance that the assays provided are correlated to the clinical efficacy of the treatment of various disorders of the claims. As can be seen from specification, the properties of the compound, which may be determined by the *in vitro* data holds significant role in determining the effective amount requirement for pharmaceutical dosage regimen to achieve the desired biological activity.

The specification provides a wide list of diverse disorders based on the inhibiting activity, see pages 1-2. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as calpain inhibitors and/or ROS trap, useful to treat a laundry list of diseases, which include inflammatory and immunological diseases, cardiovascular and cerebrovascular diseases, disorders of the

central or peripheral nervous system, proliferative diseases, autoimmune and viral diseases, cancer, etc. Test assays and procedures are provided in the specification in pages 38-40 related to inhibition of calpains and it was concluded that the compounds of the invention exhibit inhibitory activity, however, there is nothing in the disclosure regarding how this test data correlates to the treatment of the diverse disorders of the instant claims. The diseases and disorders encompassed by the instant claims include various types of cancer, inflammatory diseases, CNS disorders, viral diseases, autoimmune diseases, etc., some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, the instant claims recite treating of diseases mediated by calpains or lipid peroxidation, and there is no disclosure regarding how all these assorted types diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat the large list of diseases embraced by the claims having diverse mechanisms or inhibits calpain and lipid peroxidation generally. Further, there is no disclosure regarding how the patient in need of the treatment requiring the specific

inhibiting activity is identified and further, how all types of the diseases having divers mechanisms are treated. The state of the art is indicative of the unpredictability of the therapeutic approach based on calpains and lipid peroxidation inhibiting activity. Wang et al. (PubMed Abstract 1994) indicate that "calpain could play a key or contributory role in the pathology of a variety of disorders, including cerebral ischemia, cataract, myocardial ischemia, muscular dystrophy and platelet aggregation. ..... At present, it is difficult to confirm the exact role of calpain in these disorders because of the lack of potent, selective and cell-permeable calpain inhibitors". A recent reference, Carragher (PubMed Abstract 2006) provides that "a major limitation to the clinical use of such inhibitors is their lack of specificity among cysteine proteases and other proteolytic enzymes".

Enablement for the scope of "treating inflammatory disease" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues

respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no

means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

The specification provides 'proliferative diseases' as an example of beneficial effect of the potential role of calpain inhibitors. A 'cancer' or 'proliferative disorder' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating or lessening the severity' effect of a 'disease' solely based on the inhibitory activity disclosed for the compounds.

It is inconceivable as to how the claimed single class of compounds can treat viral diseases generally. For example, there is no known common therapeutic mechanism for viral diseases generally. There are more than 400 distinct viruses that infect humans producing a wide range of diseases. The Merck Manual of Diagnosis and Therapy states that "Several hundred different viruses infect humans. Because many have been only recently recognized, their clinical effects are not fully understood" and "Only a few viral diseases can be diagnosed clinically or epidemiologically" see <http://www.merck.com/mrkshared/mmanual/section13/chapter162/162a.jsp>. Cecil Textbook of Medicine states that "for many viral infections, no specific therapy exists. Proper use of antivirals requires specific viral diagnosis" (see the enclosed article, page 1742).

Further, the list of the diseases in the specification includes 'neurodegenerative diseases' which covers diverse disorders such as Alzheimer's disease, dementia, hereditary cerebellar ataxias, paraplegias, syringomyelia, phakomatoses, and much more. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). For example, Alzheimer's disease has traditionally been

very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease." (pg. 1994).

'Cardiovascular and cerebrovascular diseases' embrace a vast array of problems, many of which are contradictory to others. For example, the term covers hypertension and hypotension. It covers various types of arrhythmias; angina pectoris', the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias, ischemic heart disease including congestive heart failure and myocardial infarction, stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCAI; elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. Not one compound -- let alone a genus of trillions of compounds, could possibly be effective against such disorders generally.

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment or prevention. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment and/or inhibition of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. In claim 1, the phrase "AA...selected from the group consisting of a natural amino acid, a natural aminoacid the side chain of which, which carries a reactive chemical function, is protected in the form of alkyl or aralkyl ester -(for the acid function)-, in the form of alkyl or aralkyl ether or alkyl or aralkyl thioether or in the form 1f alkyl or aralkyl ester –(for the alcohol and thiol functions)- and finally an amino acid of the formula..." is not clear. The definition of AA appears to be garbled. It is unclear what "for the acid function" mean, what "form 1f" mean etc. What is reactive chemical function in the form of alkyl or aralkyl ester? What is in the form of alkyl mean? It is recommended that applicants review the definition of AA and recite specific substituents for natural aminoacid.

Note that there are three definitions of R^{15}. Is this a typo? No definition for R^{16}.

b. In claim 1, the phrase "-$(AA)_2$- also being able to be a carbapeptide" is not clear. What does this mean? What is covered by carbapeptide and what is not? What is the definition of -$(AA)_2$- if it is not carbapeptide? What is the definition of $(AA)_3$?

c. In claim 1, the phrase "R is selected from the groups consisting of hydrogen, alkyl and –CO- R^{19} in which R^{19} is alkyl" is not clear. What is the relation between the definitions of R and R^{19}? There is no R^{19} in the chemical structure or it is not part of any definition of any of the variables that correspond to the chemical structure.

Double Patenting

4. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

5. Claims 1-3 and 11-14 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-3 and 11-14 of copending Application No. 11/115,480. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Note that there is no independent definition for variable R^{16} in said copending application and there is a typographical error in the definition of R^{15}.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-4 and 11-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 11-14 of copending Application No. 11/115,480. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is significant overlap between the instant claims and the claims of the copending application. Note that all the species recited in claim 4 of the copending application 11/115,480 are present in the instant claim 4.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

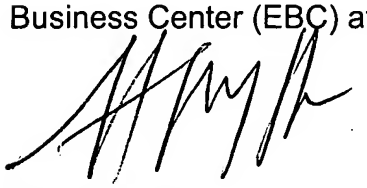
Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte whose telephone number is (571)-272-0667. The examiner can normally be reached on M-F (9.00- 5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kahsay Habte
Primary Examiner
Art Unit 1624

February 21, 2007